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(54) Title: PELLETS HAVING A CORE COATED WITH A LIPID LOWERING AGENT AND A POLYMER

(57) Abstract

The present invention is concerned with pellets comprising a 250–1180μm (16–60 mesh) sugar sphere, a coating film of a water–soluble polymer and a sparingly soluble lipid lowering agent, and a seal coating layer; pharmaceutical dosage forms comprising said pellets and a method of preparing said pellets.

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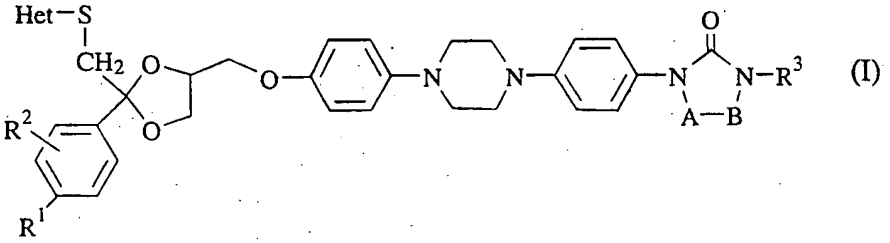
PELLETS HAVING A CORE COATED WITH A LIPID LOWERING AGENT AND A POLYMER

The present invention is concerned with pellets comprising a 250 - 1180 μm (16 - 60 mesh) sugar sphere, a coating film of a water-soluble polymer and a sparingly soluble lipid lowering agent, and a seal coating layer; pharmaceutical dosage forms comprising said pellets and a method of preparing said pellets. Lipid lowering agents can be administered to a mammal suffering from hyperlipidemia, obesitas or atherosclerosis whereby a single such dosage form can be administered once daily.

The development of efficaceous pharmaceutical compositions of lipid lowering agents such as previously disclosed in WO-96/13499, is hampered considerably by the fact that said lipid lowering agents are only very sparingly soluble in water.

The lipid lowering agents previously disclosed in WO-96/13499 have the formula



(I)

the *N*-oxides, one or more stereochemically isomeric forms, and the pharmaceutically acceptable acid addition salts thereof,

wherein A and B taken together form a bivalent radical of formula :

-N=CH-	(a),	-CH=CH-	(d),
-CH=N-	(b),	-C(=O)-CH_2-	(e),
-CH_2-CH_2-	(c),	-CH_2-C(=O)-	(f),

wherein in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C_{1-6}alkyl; and wherein in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C_{1-6}alkyl;

R^1 is hydrogen, C_{1-6}alkyl or halo;

R^2 is hydrogen or halo;

R^3 is hydrogen; C_{1-8}alkyl; C_{3-6}cycloalkyl; or C_{1-8}alkyl substituted with hydroxy, oxo, C_{3-6}cycloalkyl or aryl;

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino or aryl; pyrimidine; pyrimidine substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino or aryl; tetrazole; tetrazole substituted with C_{1-6}alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; oxadiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino; thiazole; thiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; and

aryl is phenyl or phenyl substituted with C_{1-6}alkyl or halo.

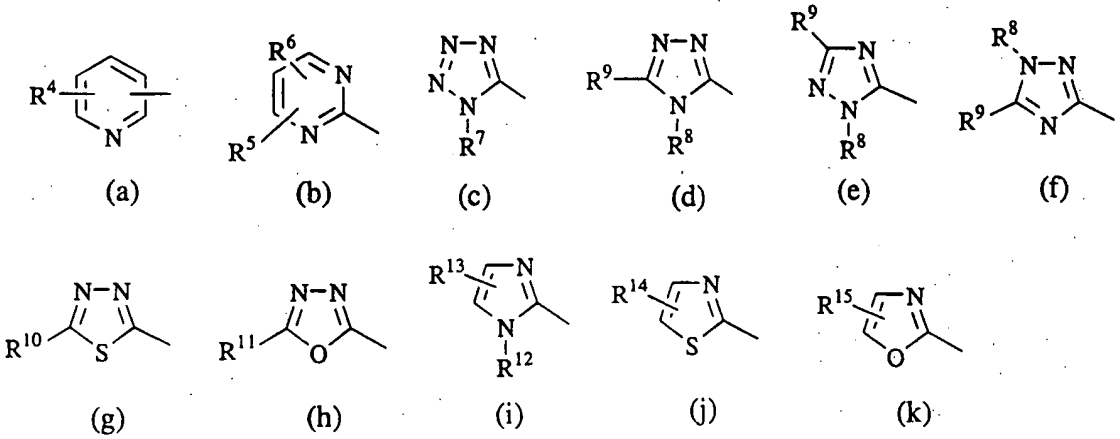
The compounds of formula (I) and their salts have very limited aqueous solubility (< 0.5 mg/ml at pH 3 [10^{-3} N HCl]) and hardly dissolve when in crystalline form. In order to ensure that the compounds of formula (I) have sufficient bioavailability, they may be dissolved in water in the presence of solubilizing agent such as a cyclodextrin derivative *e.g.* 2-hydroxypropyl-beta-cyclodextrin. The present invention provides an alternative that does not require the use of a solubilizing agent and still provides a dosage form having sufficient bioavailability.

In the compounds of formula (I) defined hereinbefore, the heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom.

As used in the foregoing definitions halo is generic to fluoro, chloro, bromo and iodo; C_{1-6}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, 1-methylethyl, 2-methylpropyl and the like; C_{1-8}alkyl defines C_{1-6}alkyl and the higher homologues thereof containing 7 or 8 carbon atoms such as, for example, heptyl

or octyl and the branched isomers thereof. C_{3-6}cycloalkyl defines saturated cyclic hydrocarbon radicals having from 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

Het may in particular be a radical of formula



(a) (b) (c) (d) (e) (f)

(g) (h) (i) (j) (k)

wherein :

R^4 is hydrogen or C_{1-6}alkyl;

R^5 and R^6 are hydrogen, C_{1-6}alkyl or amino;

R^7 is hydrogen or C_{1-6}alkyl;

each R^8 independently is hydrogen or C_{1-6}alkyl;

each R^9 independently is hydrogen, C_{1-6}alkyl, trifluoromethyl, amino or hydroxy;

R^{10} and R^{11} each independently are hydrogen or C_{1-6}alkyl;

R^{13} is hydrogen or C_{1-6}alkyl;

R^{14} is hydrogen, C_{1-6}alkyl or hydroxy;

R^{15} is hydrogen or C_{1-6}alkyl.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric ; nitric ; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids. The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such

solvates are for example hydrates, alcoholates and the like. Conversely the salt form can be converted by treatment with alkali into the free base form.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms in which the compounds of formula (I) may exist, thus, also including all enantiomers, enantiomeric mixtures and diastereomeric mixtures. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. The same applies to the intermediates as described herein, used to prepare endproducts of formula (I).

Pure enantiomeric forms of the compounds of formula (I) are defined as enantiomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds.

Asymmetric centers have ether the R- or the S-configuration. The terms *cis* and *trans* are used herein in accordance with Chemical Abstracts nomenclature and refer to the position of the substituents on a ring moiety, more in particular on the dioxolane ring in the compounds of formula (I). In the latter instance, when establishing the *cis* or *trans* configuration, the substituent with the highest priority on the carbon atom in the 2 position of the dioxolane ring, and the substituent with the highest priority on the carbon atom in the 4 position of the dioxolane ring are considered (the priority of a substituent being determined according to the Cahn-Ingold-Prelog sequence rules). When said two substituents with highest priority are at the same side of the ring then the configuration is designated *cis*, if not, the configuration is designated *trans*.

The compounds of formula (I) wherein the stereogenic carbon atom in the 2-position of the dioxolane moiety has the S-configuration are particularly preferred.

The compounds of formula (I) may also exist in their tautomeric forms. For instance, heterocycles such as, for example, pyridine, pyrimidine, triazole, thiadiazole, oxadiazole, imidazole, thiazole and oxazole, which are substituted with hydroxy, amino or C_{1-6}alkylamino may exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the

so-called *N*-oxide, particularly those *N*-oxides wherein one or more of the piperazine-nitrogens are *N*-oxidized.

Interesting compounds are those compounds of formula (I) wherein R^1 is chloro or fluoro, especially chloro.

Further interesting compounds are those compounds of formula (I) wherein R^1 is C_{1-6}alkyl, especially methyl.

Other interesting compounds are those compounds of formula (I) wherein R^2 is hydrogen, chloro or fluoro, preferably hydrogen.

Yet another group of interesting compounds of formula (I) are those compounds wherein the bivalent radical -A-B- is -CH=CH-, -N=CH- or -CH=N-, especially -CH=N- or -N=CH-. In said bivalent radicals, the hydrogen atom may be replaced by C_{1-6}alkyl, especially methyl.

A group of particular compounds comprises those compounds wherein R^3 is C_{1-8}-alkyl or C_{3-6}cycloalkyl, preferably butyl, pentyl or cyclopentyl.

A group of preferred compounds of formula (I) comprises those compounds wherein Het is a triazole, substituted triazole, imidazole, substituted imidazole, thiazole, or substituted thiazole.

More preferred compounds of formula (I) are those interesting or particular compounds wherein Het is 2-thiazolyl, 4-methyl-4*H*-1,2,4-triazol-3-yl, 4*H*-1,2,4-triazol-3-yl, 2-methyl-2*H*-1,2,4-triazol-3-yl or 2*H*-1,2,4-triazol-3-yl.

The most preferred compounds are :

cis-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3*H*-1,2,4-triazol-3-one; more in particular the diastereoisomer (-)-[2S-[2α, 4α(S*)]] compound 40 in table 3, which is referred to as Compound A hereinafter ;

cis-2-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-4-(1-methyl-propyl)-3*H*-1,2,4-triazol-3-one;

cis-2-[4-[4-[4-[[2-(4-fluorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-4-cyclopentyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one;

cis-2-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-4-pentyl-3*H*-1,2,4-triazol-3-one;
cis-4-(1-ethylpropyl)-2-[4-[4-[4-[[2-(4-fluorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one; a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

In view of their apolipoprotein B inhibiting activity and concomitant lipid lowering activity, the present compounds are useful as a medicine especially in a method of treating patients suffering from hyperlipidemia, obesitas or atherosclerosis. In particular the present compounds may be used for the manufacture of a medicine for treating disorders caused by an excess of very low density lipoproteins (VLDL) or low density lipoproteins (LDL), and especially disorders caused by the cholesterol associated with said VLDL and LDL.

A large number of genetic and acquired diseases can result in hyperlipidemia. They can be classified into primary and secondary hyperlipidemic states. The most common causes of the secondary hyperlipidemias are diabetes mellitus, alcohol abuse, drugs, hypothyroidism, chronic renal failure, nephrotic syndrome, cholestasis and bulimia. Primary hyperlipidemias are common hypercholesterolaemia, familial combined hyperlipidaemia, familial hypercholesterolaemia, remnant hyperlipidaemia, chylomicronaemai syndrome, familial hypertriglyceridaemia. The present compounds may also be used to prevent or treat patients suffering from obesitas or from atherosclerosis, especially coronary atherosclerosis and more in general disorders which are related to atherosclerosis, such as ischaemic heart disease, peripheral vascular disease, cerebral vascular disease. The present compounds may cause regression of atherosclerosis and inhibit the clinical consequences of atherosclerosis, particularly morbidity and mortality.

The dosage depends on the particular compound of formula (I) used and its formulation, the particular condition being treated and the severity thereof, the age, weight and general physical condition of the patient and whether the patient is fasting or is fed, as well as other medication the patient may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated patient and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereunder are therefore guidelines only.

Those of skill in the treatment of hyperlipidemia, obesitas or atherosclerosis can determine an effective daily amount of Compound A from the test results presented hereinafter. In general, a therapeutically effective dose will range from 0.01 mg/kg to 5 mg/kg body weight, more preferably from 0.1 mg/kg to 3 mg/kg body weight. It suffices to administer a single dose orally once daily. Said once daily dose is preferably formulated as a unit dosage form, for example, containing 25 mg to 200 mg, and in particular 100 to 150 mg of Compound A per unit dosage form.

As already mentioned, the compounds of formula (I) and their salts have a very limited aqueous solubility and hardly dissolve when in crystalline form. They may be dissolved in water in the presence of a solubilizing agent such as cyclodextrin derivative. It is highly desirable, however, to have solid pharmaceutical dosage forms of the compounds of formula (I) besides liquid formulations. Dosage forms with a high drug content, one unit of which contains the required daily dose of the active ingredient instead of two or more such units, are another desirable goal in the pharmaceutical development. Ideally, the bioavailability of dosage forms should be independent of food taken in or fasting by the patient in order that the medicament can be administered to the patient - or for that matter, to any mammal - at any time of the day, in particular that it can be administered to patients (mammals) in a fasted state. The present invention provides a once daily (o.d.) solid dosage form of a compound of formula (I) that has nearly equal bioavailability in fasted and in fed volunteers.

At this stage, it may be remarked that therapeutically effective plasma levels of the lipid lowering agent or active metabolites thereof are maintained easily for at least 24 hours. The main condition is that the lipid lowering agent must reach the plasma. The absorption of dissolved lipid lowering agent from the stomach is in itself not a problem. Thus, there is no need for a sustained release dosage form of compound of formula (I), an immediate release form will do just as well. In other words, the main problem with the administration of a lipid lowering agents in therapeutically effective amounts is in the first place concerned with ensuring that a sufficient amount of lipid lowering agent remains in solution sufficiently long enough to allow it to get into the circulation, and that it does not convert into a form that is not readily bioavailable, in particular into crystalline lipid lowering agent (which forms, for example, when lipid lowering agent precipitates in an aqueous medium).

The present invention provides pharmaceutical compositions of a lipid lowering agent and a water-soluble polymer which can be administered to a mammal, in particular a

human, suffering from hyperlipidemia, obesitas or atherosclerosis whereby a single such dosage form can be administered once daily. The bioavailability of the drug from these dosage forms in fasted and in fed mammals is comparable. The dosage forms comprise a therapeutically effective amount of pellets as described in detail hereunder.

In order to achieve the desired lipid lowering effect, it is essential that therapeutically effective plasma levels of the agent can be maintained. As the agent is practically insoluble, effective formulations should be designed in such a manner that the drug is readily bioavailable. In other words, the main problem with the administration of the agent in therapeutically effective amounts is concerned with ensuring that a sufficient amount of the agent remains in solution sufficiently long to allow it to get into the circulation, and does not convert into a form that is not readily bioavailable, in particular crystalline agent (which is formed for example when the agent precipitates in an aqueous medium). To that purpose the agent is preferably ingested during or at the end of a meal. This, however, limits the ease with which the patients can comply with their prescribed therapy ; for example, some patients are not able to eat normally or swallow medicaments easily because of illness, nausea or because of opportunistic infections of the esophagus. It would therefore be highly desirable to have pharmaceutical dosage forms which can be administered to a patient at any time of the day independently of food taken in, i.e. dosage forms which can be administered to patients in a fasted state.

Unexpectedly, it has now been found that pellets with good bioavailability of a lipid lowering agent can conveniently be manufactured. A therapeutically effective amount of novel pellets as described in detail hereunder can be filled into capsules or may be processed into tablets.

In particular the present invention is concerned with pellets which comprise (a) a central, rounded or spherical core, (b) a coating film of a water-soluble polymer and an lipid lowering agent and optionally (c) a seal-coating polymer layer, and wherein the core has a diameter of about 250 to about 1180 µm (16-60 mesh), preferably of about 300 to about 1000 µm (18-50 mesh), more preferably of about 355 to about 850 µm (20-45 mesh), and optimally of about 600 to about 710 µm (25-30 mesh).

Pellets, beads or cores of the dimensions mentioned herein can be obtained by sieving through nominal standard test sieves as described in the CRC Handbook, 64th ed., page F-114. Nominal standard sieves are characterized by the mesh/hole width (µm), DIN 4188 (mm), ASTM E 11-70 (No), Tyler® (mesh) or BS 410 (mesh) standard values.

Throughout this description and the claims, particle sizes are designated by reference to the mesh/hole width in μm and to the corresponding Sieve No in the ASTM E11-70 standard.

Materials suitable for use as cores in the pellets according to the present invention are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions (about 16-60 mesh) and firmness. Examples of such materials are polymers e.g. plastic resins; inorganic substances, e.g. silica, glass, hydroxyapatite, salts (sodium or potassium chloride, calcium or magnesium carbonate) and the like; organic substances, e.g. activated carbon, acids (citric, fumaric, tartaric, ascorbic and the like acids), and saccharides and derivatives thereof. Particularly suitable materials are saccharides such as sugars, oligosaccharides, polysaccharides and their derivatives, for example, glucose, rhamnose, galactose, lactose, sucrose, mannitol, sorbitol, dextrin, maltodextrin, cellulose, microcrystalline cellulose, sodium carboxymethyl cellulose, starches (maize, rice, potato, wheat, tapioca) and the like saccharides.

A particularly preferred material suitable for use as cores in the pellets according to the present invention is represented by 25-30 mesh sugar spheres (USP 22 / NF XVII, p. 1989) which consist of 62.5% - 91.5% (w/w) sucrose, the remainder being starch and possibly also dextrines, and which are pharmaceutically inert or neutral. Consequently, these cores are also known in the art as neutral pellets.

Pellets obtainable from 25-30 mesh sugar cores comprise approximately, by weight based on the total weight of the pellet : (a) 20 to 60 percent core material; (b) 25 to 50 percent water-soluble polymer; (c) 10 to 25 percent lipid lowering agent; and (d) 2 to 5 percent seal coating polymer.

The water-soluble polymer in the pellets according to the present invention is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution. For example, the water-soluble polymer can be selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,

- carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
- carboxyalkylcellulose esters,
- starches,
- pectines such as sodium carboxymethylamylopectine,
- chitine derivates such as chitosan,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, traganth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing pellets according to the present invention.

The drug coating layer preferably comprises a water-soluble polymer such as hydroxypropyl methylcellulose (Methocel®, Pharmacoat®), methacrylate (Eudragit E®), hydroxypropylcellulose (Klucel®), or a polyvidone. Preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. Said HPMC contains sufficient hydroxypropyl and methoxy groups to render it water-soluble. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water-soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxypropyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule. Hydroxypropyl methylcellulose is the United States Adopted Name for hypromellose (see Martindale, The Extra Pharmacopoeia, 29th edition, page 1435). Preferably hydroxypropyl methylcellulose with low viscosity, i.e. about 5 mPa.s, is used, e.g. hydroxypropyl methylcellulose 2910 5 mPa.s. In the four digit number "2910", the first two digits represent the approximate percentage of methoxyl groups and the third and fourth digits the approximate percentage composition of hydroxypropoxyl groups. 5 mPa.s is a value indicative of the apparent viscosity of a 2 % aqueous solution at 20°C.

Suitable HPMC include those having a viscosity from about 1 to about 100 mPa.s, in particular form about 3 to about 15 mPa.s, preferably about 5 mPa.s The most preferred type of HPMC having a viscosity of 5 mPa.s. is the commercially available HPMC 2910 5 mPa.s.

PVP-VA 64 is a vinylpyrrolidone - vinylacetate copolymer that is soluble in both water and alcohol, and is commercially available as Kollidon® VA 64 from BASF. The co-polymer is derived from 1-vinyl-2-pyrrolidone and vinylacetate in a ratio of 6:4 by mass, and it is designated CAS nr 25086-89-9. The copolymer is particularly suited for use as a matrix material for rapid release formulations and can be melted and extruded readily with drugs having relatively poor bioavailability to form dispersions that dissolve rapidly.

The weight-by-weight ratio of (a) : (b) is in the range of 1 : 1 to 1 : 35, preferably 1 : 1 to 1 : 5. In the case of (Compound A) : (HPMC 2910 5 mPa.s), said ratio may range from about 1 : 1 to about 1 : 3, and optimally is about 2 : 3. The weight by weight ratio of lipid lowering agent to other water-soluble polymers may be determined by a person skilled in the art by straightforward experimentation. The lower limit is determined by practical considerations. Indeed, given the therapeutically effective amount of lipid lowering agent (from about 25 mg to about 200 mg, preferably about 150 mg per day), the lower limit of the ratio is determined by the maximum amount of mixture that can be processed into one dosage form of practical size. When the relative amount of water-soluble polymer is too high, the absolute amount of mixture needed to reach the therapeutic level will be too high to be processed into one capsule or tablet. Tablets, for example, have a maximum weight of about 1 g, and the extrudate can account for maximally about 90 % (w/w) thereof. Consequently, the lower limit of the amount of lipid lowering agent over water-soluble polymer will be about 1 : 35 (25 mg lipid lowering agent + 875 mg water-soluble polymer).

On the other hand, if the ratio is too high, this means the amount of lipid lowering agent is relatively high compared to the amount of water-soluble polymer, then there is the risk that the lipid lowering agent will not dissolve sufficiently in the water-soluble polymer, and thus the required bioavailability will not be obtained. The degree to which a compound has dissolved into a water-soluble polymer can often be checked visually : if the extrudate is clear then it is very likely that the compound will have dissolved completely in the water-soluble polymer. The 1 : 1 upper limit is determined by the fact that above said ratio it was observed that the extrudate resulting from extruding lipid lowering agent with HPMC 2910 5 mPa.s forms a solid solution, but

appears to crystallize partially during milling. It will be appreciated that the upper limit of 1 : 1 may be underestimated for particular water-soluble polymers. Since this can be established easily but for the experimentation time involved, solid dispersions wherein the ratio (a) : (b) is larger than 1 : 1 are also meant to be comprised within the scope of the present invention.

The drug coating layer of the pellets as described hereinabove may further comprise one or more pharmaceutically acceptable excipients such as, for example, plasticizers, flavors, colorants, preservatives and the like. Said excipients should be inert, in other words, they should not show any degradation or decomposition under the manufacturing conditions.

In the current Compound A: HPMC 2910 5 mPa.s formulations, the amount of plasticizer is preferably small, in the order of 0 % to 15 % (w/w), preferably less than 5 % (w/w), most preferably 0 % (w/w). With other water-soluble polymers though, plasticizers may be employed in different, often higher amounts. Suitable plasticizers are pharmaceutically acceptable and include low molecular weight polyalcohols such as ethylene glycol, propylene glycol, 1,2 butylene glycol, 2,3-butylene glycol, styrene glycol; polyethylene glycols such as diethylene glycol, triethylene glycol, tetraethylene glycol; other polyethylene glycols having a molecular weight lower than 1,000 g/mol; polypropylene glycols having a molcular weight lower than 200 g/mol; glycol ethers such as monopropylene glycol monoisopropyl ether; propylene glycol monoethyl ether; diethylene glycol monoethyl ether; ester type plasticizers such as sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, allyl glycollate; and amines such as monoethanol-amine, diethanolamine, triethanolamine, monoisopropanolamine; triethylenetetramine, 2-amino-2-methyl-1,3-propanediol and the like. Of these, the low molecular weight polyethylene glycols, ethylene glycol, low molecular weight polypropylene glycols and especially propylene glycol are preferred.

A seal coating polymer layer is applied to the drug coated cores to prevent sticking of the pellets which would have the undesirable effect of a concomitant decrease of the dissolution rate and of the bioavailability. Preferably, a thin layer of polyethylene glycol (PEG), in particular polyethylene glycol 20000 (Macrogol 20000) is used as a seal coating polymer layer.

The preferred pellets comprise approximately : (a) 41 to 44 percent sugar spheres ; (b) 32 to 33 percent hydroxypropyl methylcellulose 2910 5 mPa.s ; (c) 21 to 24 percent Compound A; and (d) 3 to 4 percent polyethylene glycol 20000.

In addition, the pellets according to the present invention may further contain various additives such as thickening agents, lubricants, surfactants, preservatives, complexing and chelating agents, electrolytes or other active ingredients, e.g. antiinflammatory agents, antibacterials, disinfectants or vitamins.

The pellets according to the present invention are conveniently prepared in the following manner. A drug coating solution is prepared by dissolving into a suitable solvent system appropriate amounts of an lipid lowering agent and a water-soluble polymer. A suitable solvent system comprises a mixture of methylenechloride and an alcohol, preferably ethanol which may be denatured, for example, with butanone. Said mixture should comprise at least 50% by weight of methylenechloride acting as a solvent for the drug substance. As hydroxypropyl methylcellulose does not dissolve completely in methylenechloride, at least 10% alcohol has to be added. Preferably a relatively low ratio of methylenechloride/alcohol is used in the coating solution, e.g. a ratio methylenechloride / ethanol ranging from 75/25 (w/w) to 45/55 (w/w), in particular about 50/50 (w/w). The amounts of solids, i.e. lipid lowering agent and water-soluble polymer, in the drug coating solution may range from 7 to 10% (w/w) and preferably is about 8.3-8.5 %.

The drug coating process (on an industrial scale) is conveniently conducted in a fluidized bed granulator (e.g. Glatt type WSG-30 or GPCG-30) equipped with a Wurster bottom spray insert (e.g. an 18 inch Wurster insert). Laboratory scale process development can be performed on a Glatt type WSG-1 with a 6 inch Wurster bottom insert. Obviously the process parameters depend on the equipment used.

The spraying rate should be regulated carefully. Too low a spraying rate can cause some spray-drying of the drug coating solution and result in a loss of product. Too high a spraying rate will cause overwetting with subsequent agglomeration. Agglomeration being the most serious problem, lower spraying rates may be used initially, to be increased as the coating process proceeds and the pellets grow larger.

The atomizing air pressure with which the drug coating solution is applied also influences the coating performance. Low atomizing air pressure results in the formation of larger droplets and an increased tendency toward agglomeration. High atomizing air pressure could conceivably carry the risk of spray drying of the drug solution, but this was found not to be a problem. Consequently, atomizing air pressure may be set at nearly maximum levels.

Fluidizing air volume can be monitored by operating the exhaust air-valve of the apparatus and should be set in such a manner that optimum pellet circulation is obtained. Too low an air volume will cause insufficient fluidization of the pellets; too high an air volume will interfere with the pellet circulation due to countercurrent air streams developing in the apparatus. In the present process optimum conditions were obtained by opening the exhaust air valve to about 50% of its maximum and gradually increasing the opening thereof to about 60% of the maximum as the coating process proceeded.

The coating process is advantageously conducted by employing an inlet-air temperature ranging from about 50°C to about 55°C. Higher temperatures may speed up the process but have the disadvantage that solvent evaporation is so rapid that the coating liquid is not spread uniformly on the surface of the pellets resulting in the formation of a drug coating layer with high porosity. As the bulk volume of the coated pellets increases, drug dissolution may decrease significantly to unacceptable levels. Obviously, the optimum process temperature will further depend on the equipment used, the nature of the core and the lipid lowering agent, the batch volume, the solvent and the spraying rate.

Parameter settings for optimum coating results are described in more detail in the example hereinafter. Running the coating process under those conditions was found to yield very reproducible results.

In order to decrease residual solvent levels in the drug coating layer, the drug coated cores can conveniently be dried in any suitable drying apparatus. Good results may be obtained using a vacuum tumbler-drier operated at a temperature from about 60°C to about 90°C, preferably about 80°C, a reduced pressure ranging from about 150-400 mbar (15-40 kPa), preferably 200-300 mbar (20-30 kPa), for at least 24 hours, preferably about 36 hours. The vacuum tumbler-drier is conveniently rotated at its minimum speed, e.g. 2 to 3 rpm. After drying, the drug coated cores may be sieved.

The seal coating polymer layer is applied to the drug coated cores in the fluidized bed granulator with Wurster bottom spray insert. The seal coating solution can be prepared by dissolving an appropriate amount of a seal coating polymer into a suitable solvent system. Such a system, is, e.g. a mixture of methylene chloride and an alcohol, preferably ethanol. The ratio of methylene chloride/alcohol used may be similar to the ratio used in the drug coating process and thus can range from about 75/25 (w/w) to

about 45/55 (w/w) and in particular is about 50/50 (w/w). The amount of seal coating polymer in the seal coating spraying solution may range from 7 to 12% (w/w) and preferably is about 10-11%. The seal coating spraying solution is advantageously stirred during the seal coating process. The parameter setting for conducting this last step is essentially similar to that used in the drug coating process. Appropriate conditions are described in more detail in the example hereinafter.

A further drying step may be required after applying the seal coating polymer layer. Excess solvents could easily be removed while operating the apparatus at the parameter settings used for about 5 to 15 minutes after the spraying had been completed.

Both the drug coating process and the seal coating process are preferably conducted under an inert atmosphere of e.g. nitrogen. The coating equipment should preferably be grounded and provided with an appropriate solvent recovery system containing an efficient condensing system.

The pellets of the present invention can be formulated into pharmaceutical dosage forms comprising a therapeutically effective amount of pellets. Although, at first instance, pharmaceutical dosage forms for oral administration such as tablets and capsules are envisaged, the pellets of the present invention can also be used to prepare pharmaceutical dosage forms e.g. for rectal administration. Preferably, the pellets are filled in hard-gelatin capsules such that an amount of, for example, 100 or 200 mg of the active ingredient is available per dosage form. For example, hard-gelatin capsules of size 0 are suitable for formulating pellets comprising 21 to 22 percent by weight lipid lowering agent, equivalent to about 100 mg active ingredient.

The drug coated and seal coated pellets may be filled in hard-gelatin capsules using standard automatic capsule filling machines. Suitable earthing and de-ionisation equipment can advantageously prevent development of electrostatic charges.

Capsule filling speed may influence weight distribution and should be monitored. Good results are obtained when operating the equipment at about 75% to 85% of the maximum speed and in many cases when operating at full speed.

Using the process parameters described above, a convenient, reproducible manufacturing method for preparing pellets comprising a 25-30 mesh core, a drug coat layer of a lipid lowering agent and a water-soluble polymer and a thin seal-coating polymer layer can be obtained. Pharmacokinetic studies showed that the thus obtained pellets have excellent dissolution and bioavailability properties.

Tablet formulations

Other dosage forms are those adapted for oral administration shaped as a tablet. They can be produced from the aforementioned pellets (seal-coated, but preferably uncoated) by conventional tabletting techniques with conventional ingredients or excipients and with conventional tabletting machines. In addition, they can be produced at low cost. As mentioned above, an effective daily dose of lipid lowering agent such as Compound A ranges from about 25 mg to about 200 mg o.d., and preferably is about 100 to about 150 mg o.d. The shape of the tablets may be round, oval or oblong. In order to facilitate the swallowing of large dosage forms by a patient, it is advantageous to give the tablets an appropriate shape. Tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape. Especially preferred are biconvex oblate tablets. As discussed hereunder in more detail, a film coat on the tablet further contributes to the ease with which it can be swallowed.

Tablets that give an immediate release of lipid lowering agent upon oral ingestion and that have good bioavailability are designed in such a manner that the tablets disintegrate rapidly in the stomach (immediate release) and that the pellets which are liberated thereby are kept away from one another so that they do not coalesce, give local high concentrations of lipid lowering agent and the chance that the drug precipitates (bioavailability). The desired effect can be obtained by distributing said pellets homogeneously throughout a mixture of a disintegrant and a diluent.

Suitable disintegrants are those that have a large coefficient of expansion. Examples thereof are hydrophilic, insoluble or poorly water-soluble crosslinked polymers such as crospovidone (crosslinked polyvinylpyrrolidone) and croscarmellose (crosslinked sodium carboxymethylcellulose). The amount of disintegrant in immediate release tablets according to the present invention may conveniently range from about 3 to about 15 % (w/w) and preferably is about 7 to 9 %, in particular about 8.5 % (w/w). This amount tends to be larger than usual in tablets in order to ensure that the pellets are spread over a large volume of the stomach contents upon ingestion. Because disintegrants by their nature yield sustained release formulations when employed in bulk, it is advantageous to dilute them with an inert substance called a diluent or filler.

A variety of materials may be used as diluents or fillers. Examples are spray-dried or anhydrous lactose, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (e.g. micro-crystalline cellulose Avicel™), dihydrated or anhydrous dibasic calcium phosphate, and others known in the art, and mixtures thereof. Preferred is a commercial spray-dried

mixture of lactose monohydrate (75 %) with microcrystalline cellulose (25 %) which is commercially availble as Microcelac™. The amount of diluent or filler in the tablets may conveniently range from about 20 % to about 40 % (w/w) and preferably ranges from about 25 % to about 32 % (w/w).

The tablet may include a variety of one or more other conventional excipients such as binders, buffering agents, lubricants, glidants, thickening agents, sweetening agents, flavors, and colors. Some excipients can serve multiple purposes.

Lubricants and glidants can be employed in the manufacture of certain dosage forms, and will usually be employed when producing tablets. Examples of lubricants and glidants are hydrogenated vegetable oils, e.g hydrogenated Cottonseed oil, magnesium stearate, stearic acid, sodium lauryl sulfate, magnesium lauryl sulfate, colloidal silica, talc, mixtures thereof, and others known in the art. Interesting lubricants and glidants are magnesium stearate, and mixtures of magnesium stearate with colloidal silica. A preferred lubricant is hydrogenated vegetable oil type I (micronized), most preferably hydrogenated, deodorized Cottonseed oil (commercially available from Karlshamns as Akofine NF ™ (formerly called Sterotex™)). Lubricants and glidants generally comprise 0.2 to 7.0 % of the total tablet weight.

Other excipients such as coloring agents and pigments may also be added to the tablets of the present invention. Coloring agents and pigments include titanium dioxide and dyes suitable for food. A coloring agent is an optional ingredient in the tablet of the present invention, but when used the coloring agent can be present in an amount up to 3.5 % based on the total tablet weight.

Flavors are optional in the composition and may be chosen from synthetic flavor oils and flavoring aromatics or natural oils, extracts from plants leaves, flowers, fruits and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, bay oil, anise oil, eucalyptus, thyme oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. The amount of flavor may depend on a number of factors including the organoleptic effect desired. Generally the flavor will be present in an amount from about 0 % to about 3 % (w/w).

As known in the art, tablet blends may be dry-granulated or wet-granulated before tabletting. The tabletting process itself is otherwise standard and readily practised by

forming a tablet from desired blend or mixture of ingredients into the appropriate shape using a conventional tablet press.

Tablets of the present invention may further be film-coated to improve taste, to provide ease of swallowing and an elegant appearance. Many suitable polymeric film-coating materials are known in the art. A preferred film-coating material is hydroxypropyl methylcellulose HPMC, especially HPMC 2910 5 mPa.s. Other suitable film-forming polymers also may be used herein, including, hydroxypropylcellulose, and acrylate-methacrylate copolymers. Besides a film-forming polymer, the film coat may further comprise a plasticizer (e.g. propylene glycol) and optionally a pigment (e.g. titanium dioxide). The film-coating suspension also may contain talc as an anti-adhesive. In immediate release tablets according to the invention, the film coat is small and in terms of weight accounts for less than about 3.5 % (w/w) of the total tablet weight.

Preferred dosage forms are those wherein the weight of the pellets ranges from 40 % to 60 % of the total weight of the total dosage form, that of the diluent ranges from 20 to 40 %, and that of the disintegrant ranges from 3 to 10 %, the remainder being accounted for by one or more of the excipients described hereinabove.

Alternative preferred dosage forms according to the present invention are those from which at least 40 % of the available lipid lowering agent dissolves within 60 minutes when such a dosage form is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following : 900 ml 0.1 N HCl, 37°C with paddles turning at 50 rpm. Tablets complying with the preceding definition can be said to have Q > 40 % (60'). Preferably, tablets according to the present invention will dissolve faster and have Q > 75 % (60'), more preferably Q > 75 % (45').

It is another object of the invention to provide a process of preparing a pharmaceutical dosage form as described hereinbefore, characterized by blending a therapeutically effective amount of pellets as described hereinbefore, with pharmaceutically acceptable excipients and compressing said blend into tablets.

Further, this invention concerns pellets as described hereinbefore, for use in preparing a pharmaceutical dosage form for oral administration to a mammal suffering from hyperlipidemia, obesitas or atherosclerosis, wherein a single such dosage form can be administered once daily to said mammal.

The invention also relates to pellets as described hereinbefore, for use in preparing a pharmaceutical dosage form for oral administration to a mammal suffering from hyperlipidemia, obesitas or atherosclerosis, wherein said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

The present invention also concerns the use of pellets according to as described hereinbefore, for the preparation of a pharmaceutical dosage form for oral administration to a mammal suffering from hyperlipidemia, obesitas or atherosclerosis, wherein a single such dosage form can be administered once daily to said mammal.

The present invention also concerns the use of pellets as described hereinbefore, for the preparation of a pharmaceutical dosage form for oral administration to a mammal suffering from hyperlipidemia, obesitas or atherosclerosis, wherein said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

The invention also relates to a method of treating hyperlipidemia, obesitas or atherosclerosis in a mammal which comprises administering to said mammal an effective amount of lipid lowering agent in a single oral dosage form which can be administered once daily.

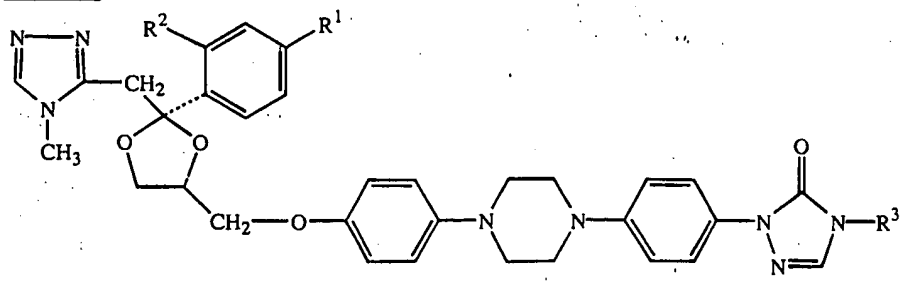
The invention also relates to a method of treating hyperlipidemia, obesitas or atherosclerosis in a mammal which comprises administering to said mammal an effective amount of lipid lowering agent in a single oral dosage form which can be administered at any time of the day independently of the food taken in by said mammal.

The invention also relates to a pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form of lipid lowering agent as described hereinbefore, and associated with said package written matter non-limited as to whether the dosage form can be taken with or without food.

Experimental part

The following tables show the formulas of the compounds of formula (I), their physical data, and references to the examples in WO-96/13499 according to which the compounds in question may be prepared. In the pharmacological example, the lipid lowering effect of the compounds of formula (I) is illustrated. Then follow examples demonstrating how Compound A (compound 40) can be converted into pellets and formulated into capsules having good bioavailability.

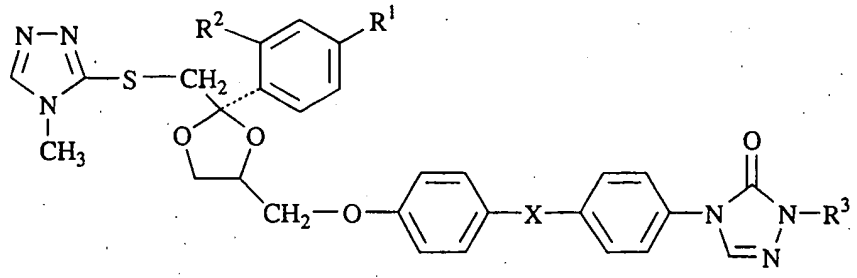
Table 1

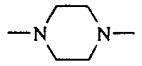
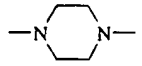
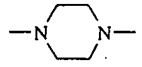
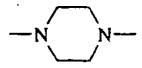
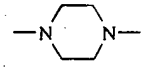
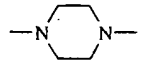
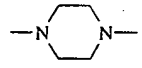
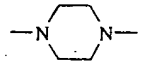
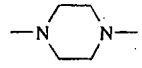
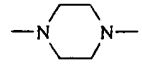
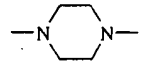
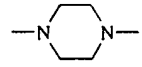
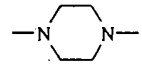
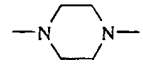
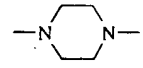


Co. No	Ex. No.	R^1	R^2	R^3	physical data
1	3	Cl	H	$CH(CH_3)2$	mp. 194.8°C / *cis*
2	3	Cl	H	$CH(CH_3)CH_2CH_3$	mp. 147.8°C/ *cis*
3	3	Cl	H	CH_2-$CH(CH_3)2$	mp. 182.5°C / *cis*
4	4	F	H	$CH(CH_3)2$	mp. 181.1°C / *cis*
5	4	F	H	CH_2-$CH(CH_3)2$	mp. 166.4°C / *cis*
6	3	Cl	H	cyclo(C_5H_9)	mp. 198.8°C / *cis*
7	3	Cl	H	$CH(CH_2CH_3)2$	mp. 139.6°C / *cis*
8	3	Cl	H	$(CH_2)2CH_3$	mp. 184.6°C / *cis*
9	4	F	H	$CH(CH_3)CH_2CH_3$	mp. 180.0°C / *cis*
10	4	F	F	$CH(CH_3)CH_2CH_3$	mp. 180.7°C / *cis*
11	4	F	H	cyclo(C_5H_9)	mp. 194.2°C / *cis*
12	4	F	H	$CH(CH_2CH_3)2$	mp. 144.3°C / *cis*
13	4	F	F	cyclo(C_5H_9)	mp. 202.4°C / *cis*
14	4	F	F	$CH(CH_2CH_3)2$	mp. 166.7°C / *cis*
15	3	Cl	H	$(CH_2)3CH_3$	mp. 194.6°C / *cis*
16	3	Cl	H	CH_2-CH_3	mp. 218.3°C / *cis*
17	3	Cl	H	CH_2-$CH(OH)$-$C(CH_3)3$	mp. 205.9°C / *cis*
18	3	Cl	H	$(CH_2)4CH_3$	mp. 173.8°C / *cis*
19	4	Cl	H	$CH(CH_3)CH_2CH_3$	mp. 140.9°C / *trans*
20	4	Cl	H	CH_3	mp. 208.6°C / *cis*
21	4	Cl	H	$CH(CH_3)CH(OH)(CH_3)$	mp. 202.4°C / *cis*
133	3	CH_3	H	$(CH_2)4CH_3$	mp. 147.4°C / *cis*
134	3	Br	H	$(CH_2)4CH_3$	mp. 152.5°C / *cis*
136	3	Cl	H	cyclo(C_5H_9)	2S-*cis*
137	3	Cl	H	$(CH_2)4CH_3$	2S-*cis*

5

Table 2



Co. No	Ex. No.	R^1	R^2	R^3	-X-	physical data
22	3	Cl	H	$CH(CH_3)CH_2CH_3$		mp. 176.9°C / *cis*
23	3	Cl	H	$CH_2CH(CH_3)2$		mp. 192.9°C/ *cis*
24	3	Cl	H	$cyclo(C_5H_9)$		mp. 210.2°C / *cis*
25	4	F	H	$CH_2CH(CH_3)2$		mp. 180.6°C / *cis*
26	3	Cl	H	$(CH_2)3CH_3$		mp. 194.1°C / *cis*
27	3	Cl	H	$(CH_2)2CH_3$		mp. 187.3°C / *cis*
28	4	F	H	$CH(CH_3)CH_2CH_3$		mp. 157.5°C / *cis*
29	4	F	F	$CH(CH_3)CH_2CH_3$		mp. 146.4°C / *cis*
30	3	Cl	H	CH_2-CH_3		mp. 195.5°C / *cis*
31	3	Cl	H	CH_3		mp. 161.2°C / *cis*
32	4	Cl	H	$(CH_2)4CH_3$		mp. 191.7°C / *cis*
33	4	Cl	H	$CH(CH_3)2$		mp. 157.2°C / *cis*
34	4	Cl	H	CH_2-$CH(OH)$-$C(CH_3)3$		mp. 189.9°C / *cis*
35	4	F	H	$cyclo(C_5H_9)$		mp. 198.2°C / *cis*
36	4	Cl	H	$CH(CH_3)CH_2CH_3$		mp. 180.7°C / *trans*

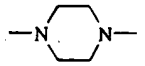
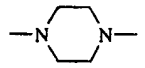
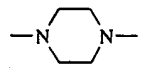
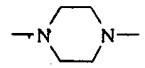
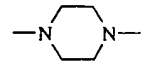
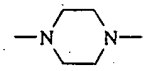
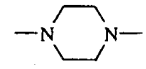
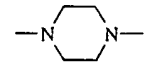
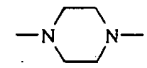
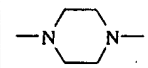
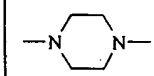
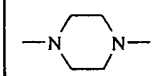
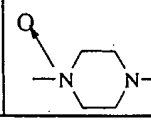
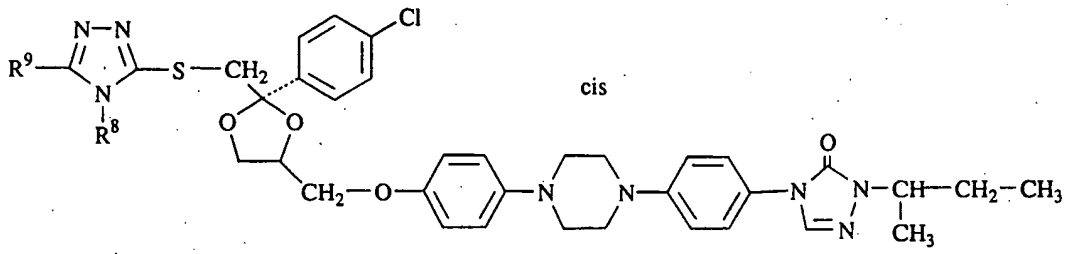
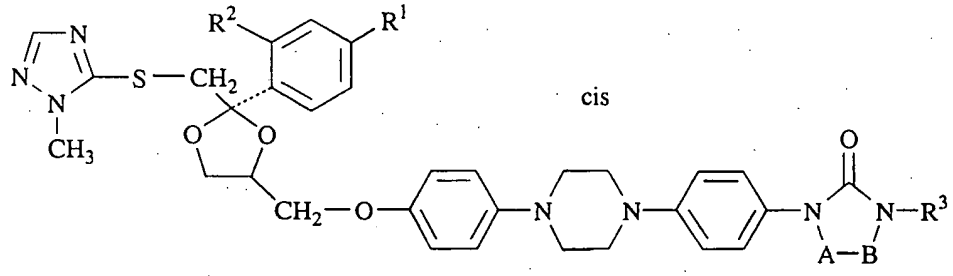
Co. No	Ex. No.	R^1	R^2	R^3	-X-	physical data
37	4	F	F	cyclo(C_5H_9)		mp. 185.2°C / *cis*
38	3	Cl	H	$CH(CH_3)CH_2CH_3$		mp. 187.0°C / $[\alpha]_D^{20}$ = -24.5° (c = 0.5% in DMF) (-)-[2S-[2α,4α(R*)]]
39	3	Cl	H	$CH(CH_3)CH_2CH_3$		mp. 155.1°C / $[\alpha]_D^{20}$ = +34.64° (c = 0.5% in DMF) (+)-[2R-[2α,4α(S*)]]
40 A	3	Cl	H	$CH(CH_3)CH_2CH_3$		mp. 156.4°C /$[\alpha]_D^{20}$ = -33.1° (c = 0.5% in DMF) (-)-[2S-[2α,4α(S*)]]
41	3	Cl	H	$CH(CH_3)CH_2CH_3$		mp. 187.7°C / $[\alpha]_D^{20}$ = +24.65° (c = 0.5% in DMF) (+)-[2R-[2α,4α(R*)]]
42	3	F	H	$(CH_2)_2CH(CH_3)_2$		mp. 176.4°C / *cis*
43	3	F	H	$CH(CH_2CH_3)_2$		mp. 145.6°C / *cis*
44	4	Cl	H	$CH(CH_2CH_3)_2$		mp. 156.7°C / *cis*
45	4	F	F	$(CH_2)_2CH(CH_3)_2$		mp. 176.8°C / *cis*
46	3	F	F	$CH(CH_2CH_3)_2$		mp. 118.6°C / *cis*
47	4	Cl	H	$CH(CH_3)COCH_3$		mp. 157.6°C / *cis*
48	6	Cl	H	$CH(CH_3)CH(OH)CH_3$		mp. 153.4°C / *cis*
135	3	Cl	H	$CH(CH_3)CH_2CH_3$		*cis*

Table 3



Co. No.	Ex. No.	R^9	R^8	physical data
49	3	CF_3	H	mp. 133.3°C
50	3	CF_3	CH_3	mp. 159.6°C
51	3	H	$(CH_2)_3CH_3$	mp. 173.5°C
52	3	H	$CH(CH_3)_2$	mp. 159.1°C
53	3	H	CH_2CH_3	mp. 175.6°C
54	3	H	$CH_2CH(CH_3)_2$	mp. 186.4°C
55	3	H	$(CH_2)_2CH_3$	mp. 168.5°C
56	3	CH_3	CH_3	mp. 170.0°C
57	3	NH_2	H	-
58	3	OH	CH_3	-
59	3	OH	$CH(CH_3)_2$	-

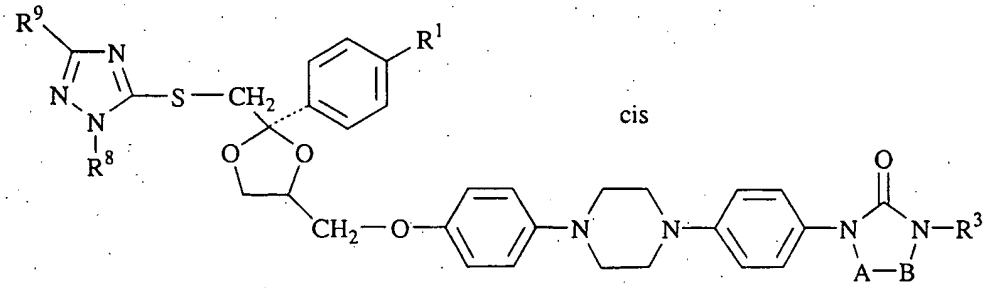
Table 4



Co. No.	Ex. No.	R^1	R^2	R^3	A-B	physical data
60	3	Cl	H	$CH(CH_3)CH_2CH_3$	CH=N	mp. 147.7°C
61	3	Cl	H	$CH_2CH(CH_3)_2$	CH=N	mp. 159.4°C
62	4	F	F	$CH(CH_3)CH_2CH_3$	CH=N	mp. 100.6°C
63	4	F	H	$CH(CH_3)CH_2CH_3$	CH=N	mp. 138.8°C
64	3	F	H	$CH(CH_2CH_3)_2$	CH=N	mp. 132.3°C
65	3	F	F	$CH(CH_2CH_3)_2$	CH=N	mp. 120.4°C

Co. No.	Ex. No.	R^1	R^2	R^3	A-B	physical data
66	3	F	H	cyclo(C_5H_9)	CH=N	mp. 163.0°C
67	3	F	F	cyclo(C_5H_9)	CH=N	mp. 150.7°C
68	3	Cl	H	$CH(CH_3)_2$	N=CH	mp. 170.1°C
69	3	Cl	H	$CH(CH_3)CH_2CH_3$	N=CH	mp. 176.2°C
70	4	F	H	$CH(CH_3)CH_2CH_3$	N=CH	mp. 157.3°C
71	4	F	F	$CH(CH_3)CH_2CH_3$	N=CH	mp. 162.4°C
72	4	F	F	cyclo(C_5H_9)	N=CH	mp. 183.3°C
73	4	F	F	$CH(CH_2CH_3)_2$	N=CH	mp. 158.9°C
74	3	F	H	cyclo(C_5H_9)	N=CH	mp. 201.2°C
75	3	F	H	$CH(CH_2CH_3)_2$	N=CH	mp. 117.4°C

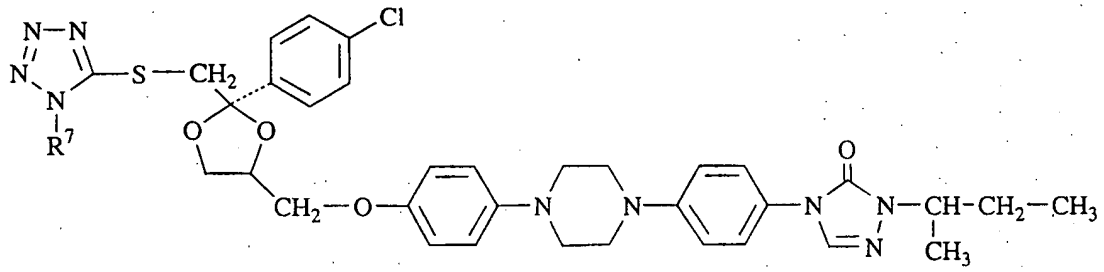
Table 5



Co. No.	Ex. No.	R^9	R^8	R^1	A-B	R^3	physical data
76	3	H	H	Cl	CH=N	$CH(CH_3)CH_2CH_3$	mp. 179.6°C
77	3	H	CH_2CH_3	Cl	CH=N	$CH(CH_3)CH_2CH_3$	mp. 119.3°C
78	3	CH_2CH_3	$(CH_2)_2CH_3$	Cl	CH=N	$CH(CH_3)CH_2CH_3$	mp. 97.8°C
79	3	H	$(CH_2)_3CH_3$	Cl	CH=N	$CH(CH_3)CH_2CH_3$	mp. 108.6°C
80	3	H	$(CH_2)_2CH_3$	Cl	CH=N	$CH(CH_3)CH_2CH_3$	mp. 87.3°C
81	3	CH_3	CH_3	Cl	CH=N	$CH(CH_3)CH_2CH_3$	mp. 85.6°C
82	5	H	$CH(CH_3)_2$	Cl	CH=N	$CH(CH_3)CH_2CH_3$	mp. 141.2°C
83	3	H	H	Cl	N=CH	$CH(CH_3)CH_2CH_3$	mp. 160.1°C
84	3	H	H	Cl	N=CH	$CH_2CH(CH_3)_2$	mp. 160.6°C
85	5	H	$CH(CH_3)_2$	Cl	N=CH	$CH(CH_3)CH_2CH_3$	mp. 134.9°C
86	3	H	H	F	CH=N	$CH(CH_3)CH_2CH_3$	mp. 101.3°C
87	3	H	CH_3	Cl	N=CH	$CH_2CH(CH_3)_2$	mp. 154.3°C
114	3	H	CH_3	Cl	CH=CH	$CH(CH_3)CH_2CH_3$	mp. 125.2°C
115	3	H	CH_3	Cl	CH=CH	$CH(C_2H_5)CH_2CH_3$	mp. 147.7°C
116	3	H	CH_3	Cl	CH=CH	cyclo(C_5H_9)	mp. 154.2°C

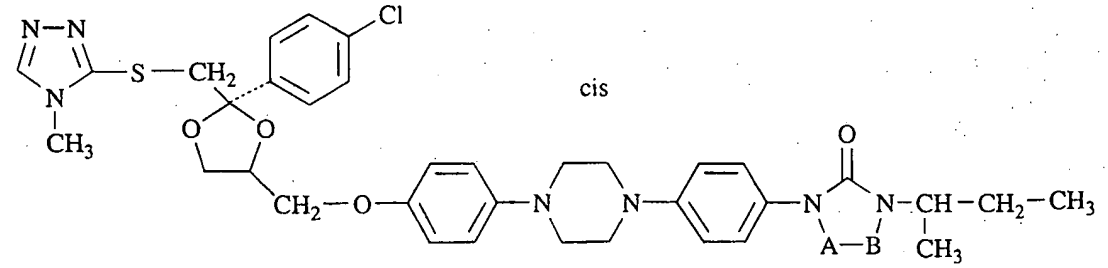
Co. No.	Ex. No.	R^9	R^8	R^1	A-B	R^3	physical data
117	3	H	H	Cl	CH=CH	$CH(CH_3)CH_2CH_3$	mp. 186.8°C
118	3	H	CH_3	F	CH=CH	$CH(C_2H_5)CH_2CH_3$	mp. 134.1°C
119	3	H	CH_3	Cl	CH=N	cyclo(C_5H_9)	mp. 161.1°C
120	5	H	$CH(CH_3)_2$	Cl	CH=CH	$CH(CH_3)CH_2CH_3$	mp. 137.5°C
121	3	H	CH_3	F	CH=CH	cyclo(C_5H_9)	mp. 166.2°C

Table 6



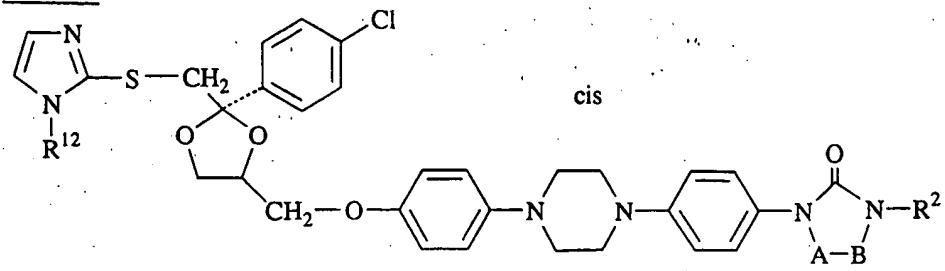
Co. No.	Ex. No.	R^7	physical data
88	3	CH_3	-
89	3	phenyl	-

Table 7



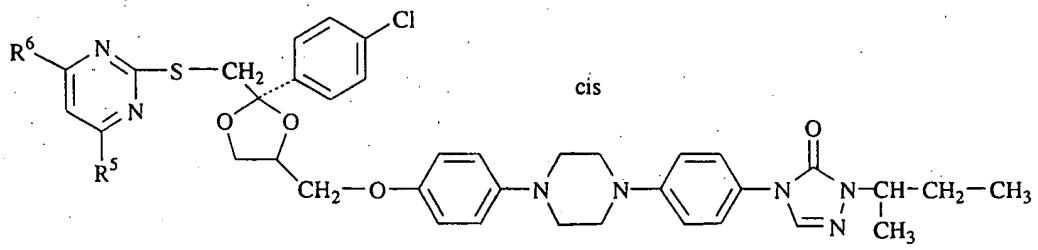
Co. No.	Ex. No.	A-B	physical data
90	3	$C(CH_3)=N$	mp. 98.3°C / 1/2 H_20
91	3	$C(CH_3)_2CO$	mp. 96.0°C
92	3	$CO-C(CH_3)_2$	mp. 127.1°C
93	4	CH=CH	mp. 171.8°C
94	4	CH_2-CH_2	mp. 147.3°C

Table 8



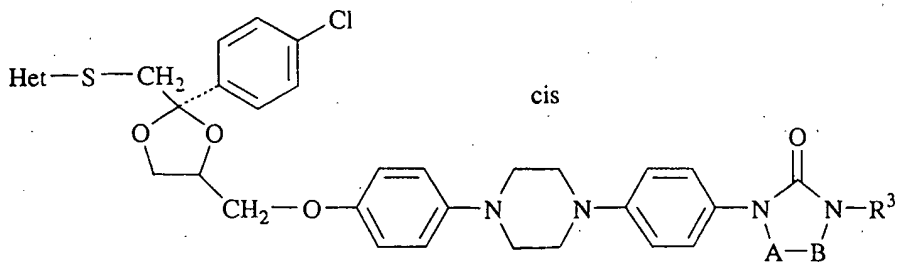
Co. No.	Ex. No.	R^{12}	A-B	R^2	physical data
95	3	CH_3	CH=N	$CH(CH_3)CH_2CH_3$	mp. 134.2°C
96	3	CH_3	CH=N	$CH_2CH(CH_3)2$	mp. 164.9°C
97	3	H	CH=N	$CH(CH_3)CH_2CH_3$	-
98	3	CH_3	N=CH	$CH(CH_3)2$	mp. 187.7°C
99	3	CH_3	N=CH	$CH(CH_3)CH_2CH_3$	mp. 150.4°C
100	3	CH_3	N=CH	$CH_2CH(CH_3)2$	mp. 146.8°C

Table 9



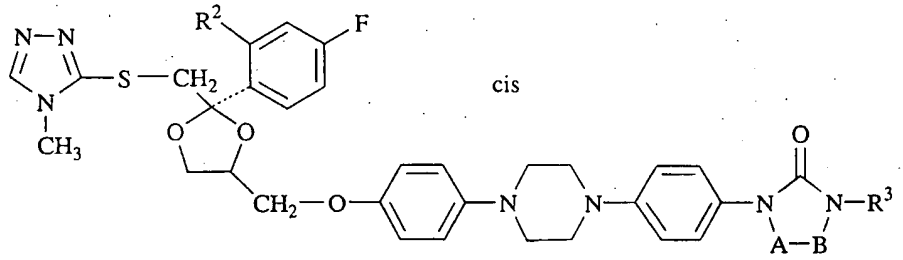
Co. No.	Ex. No.	R^5	R^6	physical data
101	3	H	H	mp. 159.6°C
102	3	CH_3	CH_3	mp. 157.4°C
103	3	NH_2	NH_2	mp. 248.5°C

Table 10



Co. No.	Ex. No.	Het	A-B	R^3	physical data
104	3	5-methyl-1,3,4-thia diazol-2-yl	CH=N	$CH(CH_3)CH_2CH_3$	-
105	3	2-pyridinyl	CH=N	$CH(CH_3)CH_2CH_3$	mp. 154.1°C
106	3	4-pyridinyl	CH=N	$CH(CH_3)CH_2CH_3$	mp. 174.9°C
107	3	4-methyl-2-oxazolyl	CH=N	$CH(CH_3)CH_2CH_3$	mp. 115.3°C
108	3	2-thiazolyl	CH=N	$CH(CH_3)CH_2CH_3$	mp. 158.6°C
109	3	4-oxo-2-thiazolyl	CH=N	$CH(CH_3)CH_2CH_3$	-
110	3	2-thiazolyl	N=CH	$CH(CH_3)CH_2CH_3$	mp. 157.8°C
111	3	2-thiazolyl	N=CH	$CH_2CH(CH_3)2$	mp. 167.9°C
112	5	(1-methylethyl)-2*H*-1,2,4-triazol-3-yl	CH=N	$CH(CH_3)CH_2CH_3$	mp. 128.8°C
113	5	(1-methylethyl)-1*H*-1,2,4-triazol-3-yl	N=CH	$CH(CH_3)CH_2CH_3$	mp. 150.0°C
122	3	4-methyl-4*H*-1,2,4-triazol-3-yl	CH=CH	$CH(C_2H_5)CH_2CH_3$	mp. 134.4°C
123	3	4-methyl-4*H*-1,2,4-triazol-3-yl	CH=CH	cyclo(C_5H_9)	mp. 202.8°C
124	5	(1-methylethyl)-1*H*-1,2,4-triazol-3-yl	CH=CH	$CH(CH_3)CH_2CH_3$	mp. 155.7°C
125	3	4-methyl-4*H*-1,2,4-triazol-3-yl	CH=N	$CH(C_2H_5)CH_2CH_3$	mp. 123.2°C

Table 11



Co. No.	Ex. No.	R^2	R^3	A-B	physical data
126	3	H	$CH(CH_3)CH_2CH_3$	CH=CH	mp. 175.4°C
127	3	F	$CH(CH_3)CH_2CH_3$	CH=CH	mp. 155.5°C
128	3	H	cyclo(C_5H_9)	CH=CH	mp. 192.0°C
129	3	F	cyclo(C_5H_9)	CH=CH	mp. 181.8°C
130	3	H	$CH(C_2H_5)CH_2CH_3$	CH=CH	mp. 145.5°C
131	3	F	$CH(C_2H_5)CH_2CH_3$	CH=CH	mp. 139.1°C
132	3	H	$(CH_2)4CH_3$	N=CH	mp. 153.1°C

Pharmacology

Example 1: Apolipoprotein B (apo B) inhibition test

Cultured human liver cells (Hep G2-cells) which synthesize and secrete low-density lipoproteins, were incubated overnight at 37 °C in a liquid medium containing radioactively labelled leucine. Thus radioactively labelled leucine was incorporated into the apolipoprotein B. The liquid medium was decanted and the apolipoprotein B was isolated by means of a double immunoprecipitation, *i.e.* first an apolipoprotein B-specific antibody (antibody$_1$) was added to the liquid medium and subsequently a second antibody (antibody$_2$) was added which binds specifically to the apoB-antibody$_1$-complex. The thus formed apoB-antibody$_1$-antibody$_2$ complex precipitated and was isolated by centrifuge. Quantification of the amount of apolipoprotein B synthesized during the night resulted from measuring the radioactivity of the isolated complex. To measure the inhibiting activity of the test compound, that test compound was added to the liquid medium at different concentrations and the concentration of apolipoprotein B synthesized in the presence of a test compound (concentration apoB(after)) was compared to the concentration of apolipoprotein B which was synthesized in the absence of the test compound (concentration apoB(control)). For each experiment the inhibition of apolipoprotein-B formation was expressed as

$$\% \text{ inhibition} = 100 \times \frac{1 - \text{concentration of apoB(after)}}{\text{concentration apoB(control)}}$$

When more experiments were carried out for the same concentration, the median value of the inhibition calculated for these experiments was calculated. IC_{50}-values (concentration of the drug needed to reduce apoB secretion to 50 % of the control) were also computed.

Table 12 lists the IC_{50}-values for some of the exemplified compounds of formula (I). Exemplified compounds of formula (I) that are not listed in Table 12, and for which data is available, have an IC_{50}-value of 1 x 10^{-6} M or more.

Table 12

Comp. No.	IC_{50} (x 10^{-8} M)
1	9.2
2	4.7
3	9.1
4	26

Comp. No.	IC_{50} (x 10^{-8} M)
54	7.9
55	7.8
56	23
58	31

Comp. No.	IC_{50} (x 10^{-8} M)
89	51
93	2.7
94	19
95	1.8

Comp. No.	IC_{50} (x 10^{-8} M)
5	20
6	12
7	7.9
8	13
9	11
12	19
13	51
15	4.8
18	4.1
22	7.1
23	14
24	5.8
28	9.7
32	18
33	9.1
35	7.7
37	23
38	6.5
40	2.3
43	11
44	5.1
49	85
50	26
51	4.7
52	25
53	8.4

Comp. No.	IC_{50} (x 10^{-8} M)
60	4.6
61	8.1
62	19
63	4.6
64	16
65	29
66	13
67	18
68	8.1
69	2.6
71	12
72	19
73	18
74	14
75	12
76	2.4
77	7.1
78	5.3
79	4.6
80	7.2
81	4.9
82	3.1
83	1.5
84	2.8
87	6.9
88	45

Comp. No.	IC_{50} (x 10^{-8} M)
96	4.7
98	2.0
99	1.5
100	2.1
101	16
102	37
105	9.9
106	88
107	4.5
108	2.6
110	2.7
111	6.2
112	98
113	3.0
114	5.3
115	5.7
116	5.8
117	1.6
118	9.1
119	4.6
121	14
122	8.8
123	7.4
126	14
128	18
130	14

Composition Example

Example 2

a) Compound A spraying solution

A stainless steel vessel was charged with methylene chloride (141 kg) and denatured ethanol (153 kg) through a filter (5 µ). Compound A (10.75 kg) and hydroxypropyl methylcellulose 2910 5 mPa.s (16.13 kg) was added while stirring. Stirring was continued until complete dissolution was obtained.

b) Seal-coating spraying solution

A stainless steel vessel was charged with methylene chloride (7.95 kg) and polyethylene glycol 20000 (Macrogol 20000) (1.935 kg) while stirring. Denatured ethanol (8.622 kg) was added and the solution was stirred until homogeneous.

c) Drug coating process

A fluidized-bed granulator (GPCG 30) equipped with a 18 inch Wurster (bottom spray) insert was loaded with 25-30 mesh (600-700 μm) sugar spheres (20.64 kg). The spheres were warmed with dry air of 50°- 55°C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 50% of its maximum in the beginning, increasing up to 60% at the end of the spraying process. The previously prepared Compound A spraying solution was then sprayed on the spheres moving in the apparatus. The solution was sprayed at an initial delivery rate of about 600 to 700 $g.min^{-1}$ at an atomizing air pressure of about 3.5 kg /cm^2 (0.343 MPa). After delivery of about 30% of the spraying solution, the delivery rate was increased to 700-800 g/min.

When the spraying process was completed, the coated spheres were dried by further supplying dry air of 50°- 55°C for about 10 minutes. The coated spheres were then allowed to cool in the apparatus by supplying dry air of 20-25°C for about 10 to 20 minutes. The apparatus was emptied and the coated spheres were collected.

d) In-between drying

In order to minimize residual solvent levels the coated spheres were then subjected to a drying step. The coated spheres were introduced in a vacuum tumbler-drier and dried for at least 24 hours, preferably about 36 hours, at a temperature of about 80°C at a pressure of about 200-300 mbar (20-30 kPa). The tumbler-drier was operated at its minimal rotation speed (2 to 3 rpm). The dried coated spheres were sieved with a sieve (Sweco S24C; sieve mesh width 1.14mm).

e) Seal-coating process

The dried coated spheres were introduced again in the fluidized-bed granulator equipped with the Wurster insert and warmed with dry air of 50 - 55°C. The previously prepared seal-coating spraying solution was then sprayed on the coated spheres moving in the apparatus. The solution was sprayed at an delivery rate of about 400 to 500 $g.min^{-1}$, at an atomizing air pressure of about 2.5 bar (0.25 MPa). When the spraying process was completed, the beads were dried by further supplying dry air of 50 - 55 °C for 10 min. The coated spheres were then allowed

to cool in the apparatus by supplying dry air of 20°-25°C for about 5 to 15 minutes. The beads were removed from the apparatus and stored in suitable containers.

f) Capsule filling

The drug coated beads were filled into hard-gelatin capsules (460 mg pellets equivalent to 100 mg active ingredient in size number 0) (115 mg pellets equivalent to 25 mg active ingredient in size number 4) using standard automatic capsule filling machines (e.g. Model GFK-1500, Höffliger and Karg. Germany). In order to obtain capsules with good weight distribution, capsule filling speed was reduced to about 75-85% of the maximum speed. Using the process parameters described above, Compound A 100 mg hard-gelatin capsules were obtained which met all the requirements, in particular the dissolution specifications.

Example 3 : Comparative bioavailability of the pellet filled capsule versus oral solution, and the influence of food.

In an open, randomised, parallel group, three-way cross-over trial, the oral bioavailability of the capsule comprising 100 mg of Compound A was compared to that of an aqueous oral solution. The aqueous oral solution comprised 0.63 mg/ml Compound A, 100 mg/ml 2-hydroxypropylcyclodextrin, 2.5 µl HCl (12 N) and NaOH to yield an end-pH of 2.0 ±0.1. Three groups of six healthy male volunteers took a single oral dose of 100 mg of Compound A in the capsule formulation under fasting conditions, directly after a standard breakfast, and as an oral solution under fasting conditions. The pharmacokinetics were assessed for the unchanged drug only and are summarized in the table hereunder.

Parameter	capsule fasting	capsule breakfast	solution fasting
t_{max}, h	1.9 ± 0.3	2.3 ± 0.6	1.3 ± 0.5
C_{max}, ng/ml	17.2 ± 12.6	45.3 ± 24.0	90.6 ± 38.7
F_{rel} C_{max}, %	17.4 ± 9.4 *	356 ±186 #	100
AUC_{∞}, ng.h/ml	148 ± 72	252 ±131	399 ±175
F_{rel} AUC_{∞}, %	27.3 ± 8.5 *	257 ±105 #	100

* : capsule fasting versus solution fasting
# : capsule fed versus capsule fasting

Claims

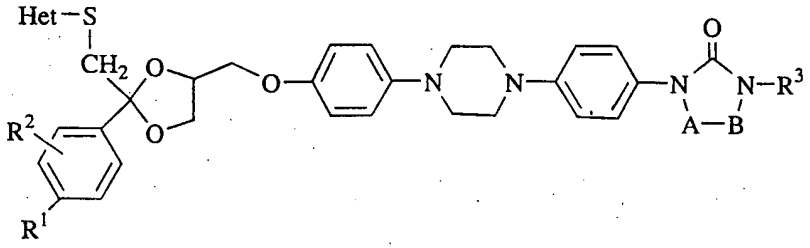
1. A pellet comprising

a) a central, rounded or spherical core having a diameter from about 250 to about 1180 μm (18-60 mesh);

b) a coating film of a water-soluble polymer and a lipid lowering agent of formula (I), and optionally

c) a seal-coating polymer layer,

characterized in that said lipid lowering agent has the formula



(I)

an *N*-oxide, a stereochemically isomeric form, a mixture of two or more such forms, or a pharmaceutically acceptable acid addition salt thereof, wherein

A and B taken together form a bivalent radical of formula :

-N=CH- (a),

-CH=N- (b),

$-CH_2-CH_2-$ (c),

-CH=CH- (d),

$-C(=O)-CH_2-$ (e),

$-CH_2-C(=O)-$ (f),

whereby in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C_{1-6}alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C_{1-6}alkyl;

R^1 is hydrogen, C_{1-6}alkyl or halo;

R^2 is hydrogen or halo;

R^3 is hydrogen; C_{1-8}alkyl; C_{3-6}cycloalkyl; or C_{1-8}alkyl substituted with hydroxy, oxo, C_{3-6}cycloalkyl or aryl;

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino or aryl; pyrimidine; pyrimidine substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino or aryl; tetrazole; tetrazole substituted with C_{1-6}alkyl or aryl; triazole;

triazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; oxadiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; thiazole; thiazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, trihalomethyl, amino, mono- or di(C_{1-6}alkyl)amino; and

aryl is phenyl or phenyl substituted with C_{1-6}alkyl or halo.

2. A pellet according to claim 1 wherein the water-soluble polymer is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution.

3. A pellet according to claim 2 wherein the water-soluble polymer is selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose,
- hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
- carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
- carboxyalkylcellulose esters,
- starches,
- pectines such as sodium carboxymethylamylopectine,
- chitin derivates such as chitosan,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, traganth, agar-agar, gummi arabicum, guar

gummi and xanthan gummi,

- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

4. A pellet according to claim 3 wherein the water-soluble polymer is hydroxypropyl methylcellulose HPMC 2910 5 mPa.s.

5. A pellet according to claim 1 wherein the weight to weight ratio of lipid lowering agent : water-soluble polymer is from 1:1 to 1:3.

6. A pellet according to claim 1 wherein the seal-coating polymer is polyethylene glycol.

7. A pellet according to claim 1 comprising by weight based on the total weight of the pellet :
   a) 20 to 60 percent core material;
   b) 25 to 50 percent water-soluble polymer;
   c) 10 to 25 percent lipid lowering agent; and
   d) 2 to 5 percent seal-coating polymer.

8. A pellet according to claim 7 comprising approximately :
   a) 41 to 44 percent sugar spheres;
   b) 32 to 33 percent hydroxypropyl methylcellulose 2910 5 mPa.s.;
   c) 21 to 22 percent *cis*-(-)-[2S-[2alpha, 4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one ; and
   d) 3 to 4 percent polyethylene glycol 20000.

9. A pellet according to anyone of the preceding claims wherein the core material is a 600 - 710 μm (25-30 mesh) sugar sphere.

10. A pellet according to anyone of the preceding claims wherein the lipid lowering agent is *cis*-(-)-[2S-[2alpha, 4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[[(4-

methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one.

11. A process for preparing pellets as claimed in any one of claims 1 to 10 characterized by,
    a) coating 250 - 1180 μm (18-60 mesh) sugar spheres by spraying onto them with a solution of a lipid lowering agent and a water-soluble polymer in an organic solvent consisting of methylene chloride and an alcohol in a fluidized-bed granulator equipped with a Wurster (bottom spray) insert;
    b) drying the resulting coated cores; and
    c) seal-coating the dried cores by spraying onto them with a solution of a seal-coating polymer in an organic solvent consisting of methylene chloride and an alcohol in a fluidized-bed granulator equipped with a Wurster (bottom spray) insert.

12. Drug-coated pellets obtainable by a process according to claim 11.

13. A pharmaceutical dosage form comprising an effective lipid lowering amount of pellets as claimed in any one of claims 1 to 10.

14. A dosage form according to claim 13 wherein the dosage form is a hard-gelatin capsule.

15. A dosage form according to claim 13 from which at least 40 % of the available lipid lowering agent dissolves within 60 minutes when said dosage form is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following : 900 ml 0.1 N HCl, pH 6.0, 37°C with paddles turning at 50 rpm.

16. Pellets according to any one of claims 1 to 10 for use in preparing a pharmaceutical dosage form for oral administration to a mammal suffering from hyperlipidemia, obesitas or atherosclerosis, wherein a single such dosage form can be administered once daily to said mammal.

17. Pellets according to any one of claims 1 to 10 for use in preparing a pharmaceutical dosage form for oral administration to a mammal suffering from hyperlipidemia,

obesitas or atherosclerosis, wherein said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

18. Use of pellets according to any one of claims 1 to 10 for the preparation of a pharmaceutical dosage form for oral administration to a mammal suffering from hyperlipidemia, obesitas or atherosclerosis, wherein a single such dosage form can be administered once daily to said mammal.

19. Use of pellets according to any one of claims 1 to 10 for the preparation of a pharmaceutical dosage form for oral administration to a mammal suffering from hyperlipidemia, obesitas or atherosclerosis, wherein said dosage form can be administered at any time of the day independently of the food taken in by said mammal.

20. A pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form of lipid lowering agent as claimed in any one of claims 13 to 15, and associated with said package written matter non-limited as to whether the dosage form can be taken with or without food.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 99/02768

A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 13499 A (JANSSEN PHARMACEUTICA) 9 May 1996 (1996-05-09) cited in the application the whole document	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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